

Base-free Enantioselective C(1)-Ammonium Enolate Catalysis Exploiting Aryloxides: A Synthetic and Mechanistic Study

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Dedication ((optional))

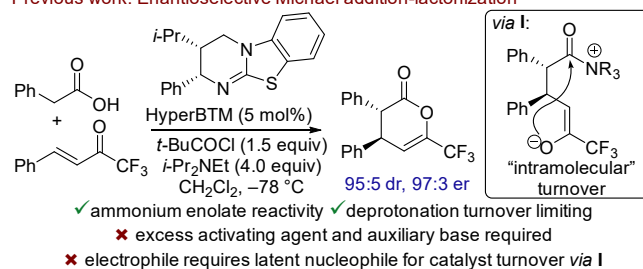
Abstract: An isothiurea-catalyzed enantioselective Michael addition of aryl ester pronucleophiles to vinyl bis-sulfones *via* C(1)-ammonium enolate intermediates has been developed. This operationally simple method allows the base-free functionalization of aryl esters to form α -functionalized products containing two contiguous tertiary stereogenic centres in excellent yield and stereoselectivity (all $\geq 99:1$ er). Key to the success of this methodology is the multifunctional role of the aryloxide, which operates as a leaving group, Brønsted base, Brønsted acid and Lewis base within the catalytic cycle. Comprehensive mechanistic studies, including variable-time normalization analysis (VTNA) and isotopologue competition experiments, have been carried out. These studies have identified (i) orders of all reactants; (ii) a turnover-limiting Michael addition step, (iii) product inhibition, (iv) the catalyst resting state and (v) catalyst deactivation through protonation.

Introduction

C(1)-Ammonium enolates^[1] have emerged as powerful catalytically-generated synthetic intermediates for enantioselective C-C and C-X bond formation. Traditionally generated from Lewis basic tertiary amine catalysts^[2] and ketenes,^[3] recent advances have sought to access C(1)-ammonium enolates directly from either carboxylic acids^[1b,4] or activated aryl esters.^[5] When using carboxylic acid starting materials, the most common approach involves *in situ* derivatization to an anhydride prior to preparation of the C(1)-ammonium enolate. Although powerful in concept, this strategy is limited in terms of sustainability and atom economy. As exemplified in Scheme 1, treatment of phenylacetic acid with excess activating agent (such as *t*-BuCOCl, 1.5 equiv.) is necessary to generate a reactive anhydride *in situ* prior to C(1)-ammonium enolate formation, while excess auxiliary base (such as *i*-Pr₂NEt, 4.0 equiv.) is required for effective catalysis.^[6] These methodologies generally require the use of an electrophile that contains a latent nucleophilic site (such as an enone), in order for catalyst turnover to be achieved through *intramolecular* cyclization to give formal cycloaddition products (Scheme 1, inset).

Building upon Lectka's pioneering work using halogenated quinones as electrophiles for the *in situ* generation of aryloxides,^[7] recent work has focused on using electron-deficient aryl esters as C(1)-ammonium enolate precursors in isothiurea

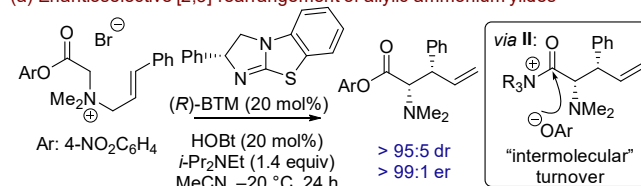
Previous work: Enantioselective Michael addition-lactonization



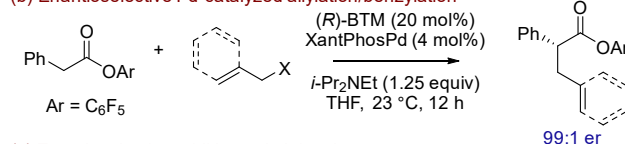
Scheme 1. Intramolecular catalyst turnover in ammonium enolate catalysis.

catalysis.^[8] In our previous work this strategy was first applied to the enantioselective [2,3]-rearrangement of allylic ammonium ylides to form stereodefined α -amino acid derivatives (Scheme 2a).^[9] In this case, aryloxide released upon addition of the Lewis base catalyst to a *para*-nitrophenyl ester substrate was used to attack the post-rearrangement acyl ammonium intermediate **II** (or its HOBt ester equivalent) and regenerate the free catalyst.^[10] Building upon this approach, Snaddon and co-workers have developed elegant α -allylation and α -benzylation protocols of pentafluorophenyl esters in union with palladium catalysis (Scheme 2b),^[11] while Hartwig and co-workers developed a co-operative isothiurea/iridium-catalyzed allylation.^[12] In previous work we reported the enantioselective addition of C(1)-ammonium enolates, generated from *para*-nitrophenyl esters, to iminium ion electrophiles, however stoichiometric tetra-*n*-butyl ammonium *para*-nitrophenoxide was also required as an

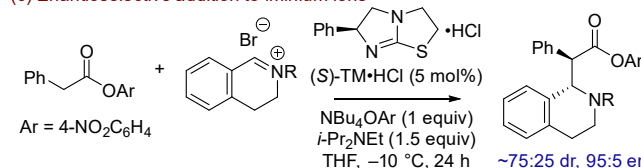
Recent advances: aryloxide promoted "intermolecular" catalyst turnover
(a) Enantioselective [2,3]-rearrangement of allylic ammonium ylides



(b) Enantioselective Pd-catalyzed allylation/benzylation



(c) Enantioselective addition to iminium ions



✗ high catalyst loadings common (20 mol%) ✗ no mechanistic analysis
✗ stoichiometric auxiliary base or additive required for optimal reactivity

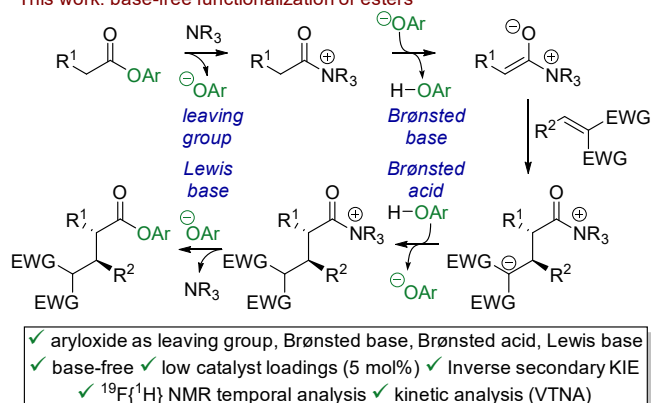
Scheme 2. Aryloxide promoted intermolecular catalyst turnover in enantioselective ammonium enolate catalysis. (HOBt: hydroxybenzotriazole).

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additive for optimal reactivity (Scheme 2c).^[13] While these impressive strategies broaden the compatibility of C(1)-ammonium enolate intermediates in dual catalytic processes and with alternative electrophilic components, all typically employ high catalyst loadings of the Lewis base (commonly 20 mol%) as well as excess auxiliary base. Furthermore, these latter processes (Scheme 2b,c) are not well-understood mechanistically in terms of identification of reaction intermediates, reaction orders with respect to components, and turnover-limiting step.

Given this background, we envisaged an alternative base-free and proton neutral Lewis base-catalyzed strategy for the catalytic enantioselective functionalization of electron-deficient aryl esters. Addition of an isothiourea Lewis base to an aryl ester would initially generate an acyl ammonium aryloxide ion pair, with deprotonation of the acyl ammonium by the aryloxide generating the reactive C(1)-ammonium enolate. Enantioselective Michael addition to a suitable acceptor, followed by proton transfer from the *in situ* generated phenol, and subsequent aryloxide turnover would deliver α -alkylated products containing two tertiary stereogenic centres (Scheme 3). This approach would circumvent the previous necessity for the addition of an auxiliary base but would require the aryloxide to fulfill the role of proton shuttle within the catalytic cycle. In this manuscript, this concept is demonstrated through the isothiourea-catalyzed Michael addition of ester pronucleophiles to bis-sulfone Michael acceptors, where the sulfone groups present within the reaction product provide functional handles for further derivatization. Mechanistic investigations have been carried out to analyze the temporal concentrations of the reaction components, with variable time normalization analysis (VTNA) used to determine their respective orders. Catalyst deactivation and product inhibition effects were also found to be significant over the reaction course. Measurement of a kinetic isotope effect (KIE) was used to identify the turnover-limiting step of the catalytic process.

This work: base-free functionalization of esters



Scheme 3 This work: base-free enantioselective ammonium enolate catalysis. (EWG: electron-withdrawing group).

Results and Discussion

1. Optimization Studies

Proof-of-principle studies commenced using *para*-nitrophenyl ester **1**, 1.1 equivalents of vinyl bis-sulfone **2** and tetramisole•HCl **3** (20 mol%) in dichloromethane at room temperature for 24 hours (Table 1, entry 1). Whilst the product ester could be isolated following chromatographic purification, it proved unstable to HPLC analysis and so all further products were isolated as the corresponding benzyl amide following addition of benzylamine at the end of the reaction. Encouragingly, amide **4** was formed in good yield (67%) with high diastereoselectivity (88:12 dr) and excellent enantioselectivity (> 99:1 er). The use of various isothiourea catalysts was next investigated. Benzotetramisole (BTM) **5** gave the product in improved yield (78%, entry 2), whilst maintaining high dr (86:14) and er (> 99:1). Using HyperBTM **6** as catalyst gave amide **4** in a lower yield of 60% yield, although excellent stereoselectivity was still observed (entry 3). Notably, consistent with our mechanistic hypothesis (Scheme 3), the use of an external base was not necessary for effective catalysis. The catalyst loading of BTM **5** could be reduced to 5 mol% whilst maintaining high diastereo- and enantioselectivity, however **4** was obtained in lower yield (54%, entry 4). Reversing the stoichiometry and increasing the ester equivalents (1.5 equiv.) and concentration (0.5 M) provided amide **4** in improved yield (entry 5). The use of alternative, industrially preferable solvents (dimethylcarbonate, *iso*-propyl acetate)^[14] provided amide **4** in comparable yields and stereoselectivity with the exception of 2-methyl THF which led to reduced yields and dr (entries 6–8).

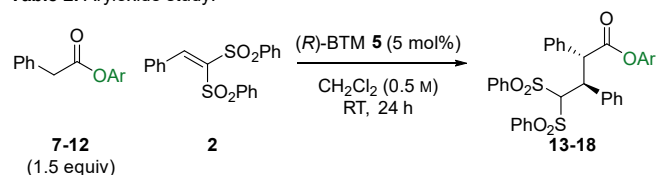
Table 1. Reaction optimization.

Entry	Catalyst (mol%)	Solvent	Yield ^a (%)	dr ^b	er ^c
1 ^d	(S)-TM•HCl (20)	CH ₂ Cl ₂	67	88:12	< 1:99
2	(R)-BTM (20)	CH ₂ Cl ₂	78	86:14	> 99:1
3	(2S,3R)-HyperBTM (20)	CH ₂ Cl ₂	60	80:20	98:2
4	(R)-BTM (5)	CH ₂ Cl ₂	54	89:11	> 99:1
5 ^e	(R)-BTM (5)	CH ₂ Cl ₂	86 (75)	89:11	> 99:1
6 ^e	(R)-BTM (5)	DMC	85	89:11	98:2
7 ^e	(R)-BTM (5)	<i>i</i> -PrOAc	89	89:11	> 99:1
8 ^e	(R)-BTM (5)	2-MeTHF	63	79:21	> 99:1

[a] Combined yield of major and minor diastereomers. Determined by ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene internal standard. Isolated yield of major diastereoisomer in parenthesis. [b] Determined by ¹H NMR analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] 1.0 equiv. *i*-Pr₂NEt added. [e] 1.5 equiv. **1**, 1.0 equiv. **2**, 0.5 M concentration. (DMC: dimethylcarbonate).

Key to this strategy is the multiple roles of the aryloxide within the catalytic cycle. It is required to be an effective leaving group for *N*-acylation, to act as a Brønsted base and a Brønsted acid (as the corresponding phenol), before acting as a Lewis base. The steric and electronic effects of the aryloxide leaving group were examined to gain insight into the subtle effects that could alter its nucleophilicity, nucleofugality and basicity (Table 2).¹⁵ Using *para*-nitrophenyl ester **7** allowed ester **13** to be isolated in high yield, dr and er (entry 1, 84%, 84:16 dr, > 99:1 er). Reaction of pentafluorophenyl ester **8** gave product **14** in lower yield (39%), although excellent stereocontrol was maintained (entry 2). The use of tetrafluorophenyl ester **9** gave product **15** in 56% yield (entry 3), whilst 3,5-bis(trifluoromethyl) ester **10** gave product **16** in 44% yield (entry 4). Interestingly, the reaction of both 2,4,6-trichlorophenyl ester **11** and the parent phenyl ester **12** showed no reactivity (entries 5 and 6). Correlation of the observed reactivity with variation in pK_a of the phenol can be identified. *para*-Nitrophenol (pK_a 7.1 in H_2O)^[16] is an efficient leaving group but is capable of the desired amphoteric behavior and promoting catalyst turnover. Pentafluorophenol (pK_a 5.53) and tetrafluorophenol (pK_a 6.0) have lower pK_a values,^[17] with the corresponding aryloxides less Brønsted basic and less nucleophilic, presumably resulting in lower concentrations of the reactive ammonium enolate. Despite 2,4,6-trichlorophenol having a comparable pK_a (5.99) to tetrafluorophenol, the lack of reactivity is presumably due to the steric demands of the *ortho*-substituents attenuating its nucleophilicity.^[18] The ester derived from phenol is less electrophilic and does not acylate the catalyst. A careful balance of leaving group ability, amphoteric behaviour and steric effects within this series indicates that *para*-nitrophenol is the most effective aryloxide for this application.

Table 2. Aryloxide study.



Entry	Substrate	Yield ^a (%)	dr ^b	er ^c
1 ^d	7	84	84:16	> 99:1
2	8	39	84:16	> 99:1
3	9	56	82:18	> 99:1
4	10	44	80:20	> 99:1
5	11	0	-	-
6	12	0	-	-

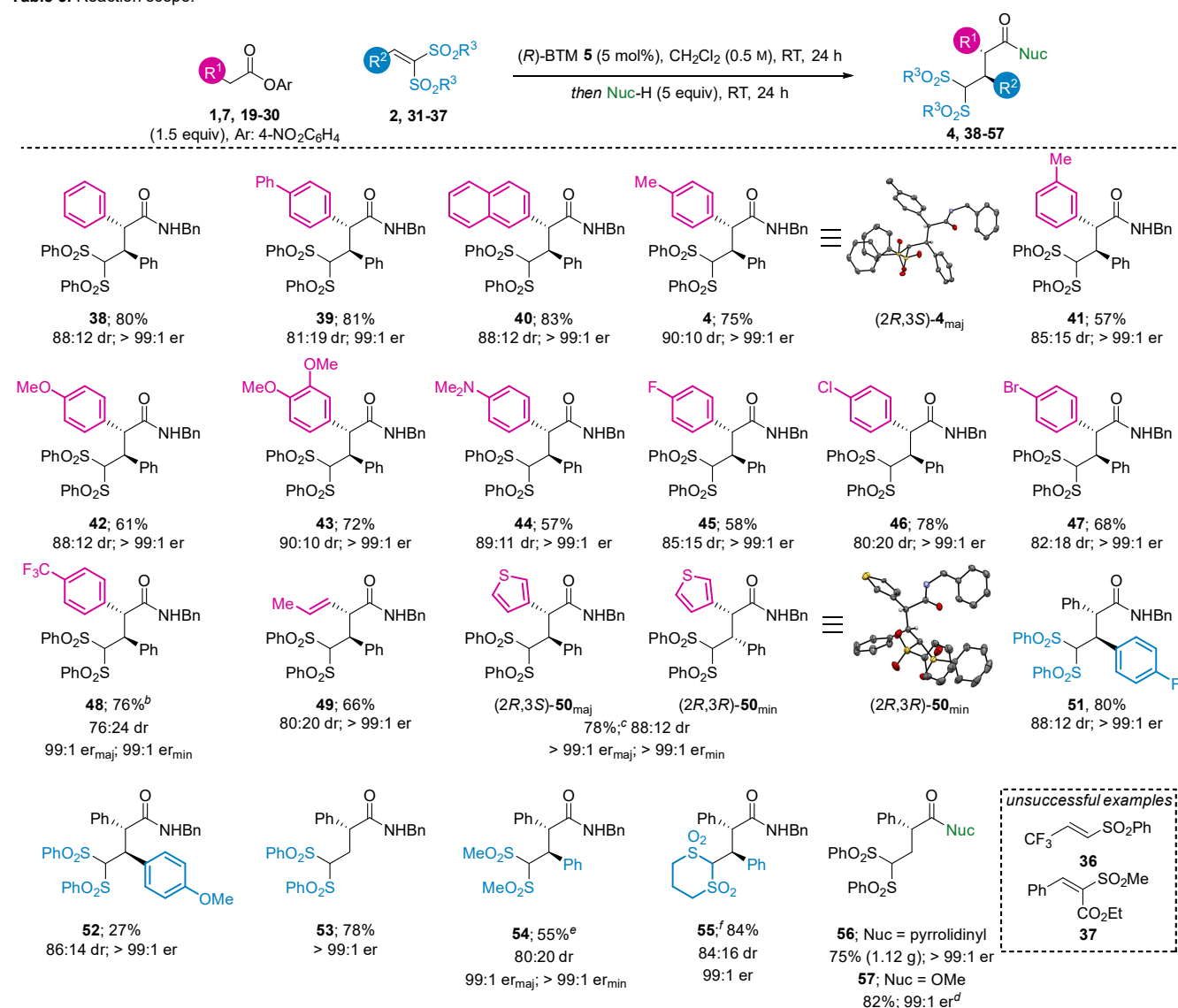
[a] Isolated yield of major diastereoisomer. [b] Determined by 1H NMR analysis of the crude reaction mixture. [c] Determined by chiral HPLC analysis after conversion to the corresponding benzyl amide. [d] Isolated as 95:5 dr.

2. Scope and Limitations

The generality of the Michael addition protocol was next investigated by exploring the scope of the ester component (Table 3). Dichloromethane proved the most general solvent for effective catalysis upon extension to alternative substrates (see SI for further details).^[19] The diastereoisomers were separable by column chromatography and the quoted yield in Table 3 refers to the isolated yield of the major diastereoisomer. Firstly, a range of substituted arylacetic *para*-nitrophenyl esters with different steric and electronic properties was explored. Electron-neutral phenyl, 4-biphenyl and 2-naphthyl groups provided the corresponding amide products **38**, **39** and **40** in high yield and diastereoselectivity, with exceptional enantiocontrol (all \geq 99:1 er). Electron-donating aryl substituents (such as 4-tolyl, 4-methoxyphenyl and 4-dimethylaminophenyl) gave the corresponding amide products **4**, **41–44** in good yield and with high diastereoselectivity (\sim 90:10 dr). The relative and absolute configuration of the major (2*R*,3*S*)-diastereoisomer **4** was determined by single crystal X-ray crystallography with all other products assigned by analogy.^[20] Halogen-substituted aryl rings gave amides **45–47** in good yield and er, although in reduced dr (\sim 80:20 dr). Introduction of the electron-withdrawing 4-trifluoromethylphenyl group gave product **48** in diminished diastereoselectivity (76:24 dr), albeit still in high yield and enantiopurity for both diastereoisomers. Epimerization studies were undertaken to probe the low diastereoselectivity (see SI); no product epimerization under the reaction conditions was observed, indicating the diastereoselectivity is derived from the orientation of the electrophile on approach.^[21] Having demonstrated a range of substituted aryl rings were compatible with the optimized conditions, attention was turned to other classes of ester. Pleasingly, alkenyl substituents were tolerated, with amide **49** obtained in 66% yield and with good stereoselectivity. Heteroaryl esters were also compatible, with 2-thiophenyl amide **50** obtained in high yield and dr; both diastereoisomers were obtained in > 99:1 er. The relative and absolute configuration within the minor (2*R*,3*R*)-diastereoisomer **50** was also determined by single crystal X-ray crystallography.^[22] This is consistent with high enantiocontrol at C(2) for both diastereoisomers, which are epimeric at C(3). Unfortunately, alkyl, α,α -disubstituted and benzyloxy esters were unreactive in this protocol, only returning starting materials,^[23] whilst *ortho*-substitution gave product in diminished yield and lower diastereoselectivity (see SI).

The scope of the developed process was further tested by variation of the electrophile component (Table 3). Firstly, the effect of the β -substituent was examined: the use of an electrophile bearing a 4-fluorophenyl substituent gave amide **51** in excellent yield, dr and er. However, substitution with an electron-donating 4-methoxyphenyl gave amide **52** in lower yield. Using the commercially available unsubstituted bis(phenylsulfonyl)ethylene electrophile provided a single enantiomer of amide **53** in high yield (78%). The scope of the electrophile was extended to alkyl sulfone groups, with methyl sulfone giving amide **54** in acceptable yield (55%). The use of a cyclic bis-sulfone allowed access to amide **55** in excellent yield, dr and er but required acetonitrile as the reaction solvent due to

Table 3. Reaction scope.

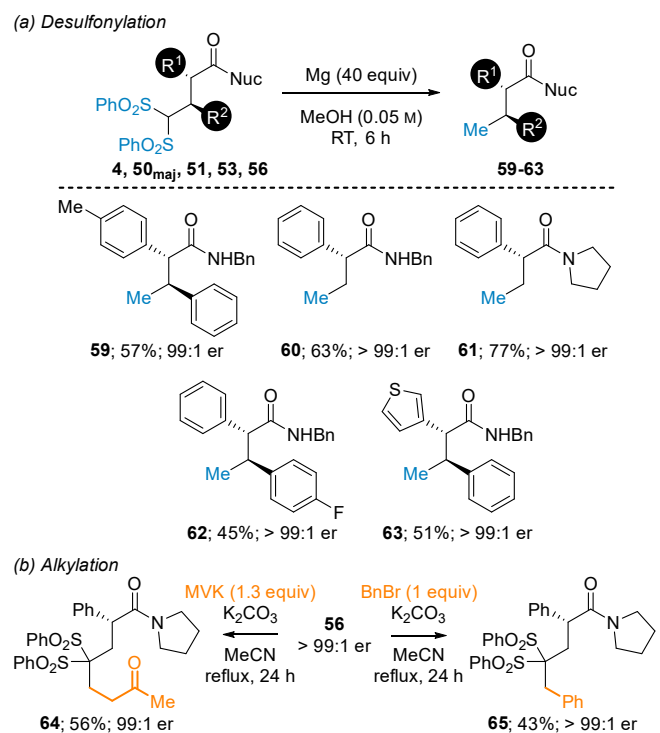


[a] dr determined by ¹H NMR analysis of the crude reaction mixture; isolated yield of a single major diastereoisomer; er determined by chiral HPLC analysis. [b] isolated > 95:5 dr. [c] combined yield of separable diastereoisomers. [d] er determined after reduction to corresponding alcohol (**58**). [e] isolated 80:20 dr. [f] MeCN as solvent.

the insolubility of the electrophile in dichloromethane. Unfortunately, Michael acceptors bearing a single sulfone group (**36**, **37**) were unreactive, presumably due to the lower electrophilicity of these acceptors. To further exemplify product diversity, the addition of alternative nucleophiles to give isolable products at the end of the reaction was investigated. Using unsubstituted bis-sulfone **33**, addition of pyrrolidine gave tertiary amide **56** in high yield and er (75%, > 99:1 er) on a 3 mmol scale, allowing the formation of 1.12 g of product. Addition of methanol provided ester **57** in excellent yield and er.

Having demonstrated the scope and limitations of this protocol, it was proposed that the sulfone functional handle in the product could be exploited to carry out further manipulations to access complex, valuable products. Following a procedure developed by Williams and co-workers,^[24] initial studies focused on desulfonation using magnesium turnings in methanol at room temperature (Scheme 4a). Desulfonation of 2,3-diphenyl

substituted amide gave anti-product **59** in good yield (57%), whilst maintaining stereointegrity (> 95:5 dr, 99:1 er). Desulfonation of pyrrolidinyl and benzyl-amides containing a single stereogenic centre was also successful, providing amides **60** and **61** in improved yield (63% and 77%). Desulfonation of 4-fluorophenyl amide **51** and thiophenyl amide **50** proved amenable to the unmasking conditions, allowing access to single enantiomers of products **62** and **63** in moderate yield. Alternatively, the pro-nucleophilic nature of the bis-sulfone moiety could be exploited to allow further functionalization (Scheme 4b). Treatment of **56** with either methyl vinyl ketone (MVK) or benzyl bromide under basic conditions gave chain extended amides **64** and **65** respectively in good yield whilst maintaining enantiopurity.



Scheme 4. Product derivatization through (a) desulfonylation and (b) alkylation. (MVK: methyl vinyl ketone).

3. Mechanistic Studies

3.1 Quantitative $^{19}\text{F}\{^1\text{H}\}$ NMR Reaction Monitoring

Having demonstrated the reaction scope, further studies sought to provide mechanistic insight into this developed methodology through kinetic analysis. Primary studies set out to identify the catalyst resting state and any potential reaction intermediates, as well as determining the reaction order with respect to each component. Quantitative reaction monitoring was achieved by *in situ* $^{19}\text{F}\{^1\text{H}\}$ NMR spectroscopy using ^{19}F -labelled ester **66** (δ_{F} –123.36), ^{19}F -labelled electrophile **31** (δ_{F} –107.64) and ^{19}F -BTM **67** (δ_{F} –122.26) in CD_2Cl_2 [0.1 M] using 1,3-difluorobenzene (δ_{F} –110.73) as an internal standard (Figure 1a). Under these conditions, the reaction time (3 h) was substantially shorter than the standard conditions (24 h) enabling facile NMR analysis over

the course of the reaction (Figure 1b) and giving product **68** in 82% yield, 88:12 dr and > 99:1 er.^[25] During the course of the reaction, both diastereoisomeric reaction products, each containing two distinct ^{19}F -environments, were observed and were distinguishable from the starting components. Monitoring the reaction over time revealed the ^{19}F chemical shift of ^{19}F -BTM **67** underwent a downfield shift (δ_{F} –122.26 to δ_{F} –121.99 ppm) during the reaction, indicative of partial protonation, and hence deactivation, of the catalyst.^[26] To account for this observation within the kinetic analysis, ^{19}F -BTM $\cdot\text{HCl}$ was synthesized as a standard (δ_{F} –115.64 ppm), allowing the concentration of free catalyst to be calculated as a function of δ_{F} (See SI).^[27] These studies are consistent with the dominant catalyst resting state being the free catalyst throughout the reaction protocol. The acyl ammonium salt of the starting ester was synthesized as both the chloride (δ_{F} –115.52) and 2-fluoro-4-nitrophenoxide (δ_{F} –111.70) counterions as potential intermediates (see SI). However, no long-lived intermediates corresponding to > 1% of the reaction mixture were observed during the reaction.^[28] A similar approach was attempted to form the acyl ammonium of the product (see SI); catalyst **67** was added to product **68**, however no acyl ammonium was observed.^[29] Whilst no significant quantities of other intermediates were detected during the analysis of this reaction, an alternative intramolecular catalyst turnover event to form a reactive, short-lived intermediate which is intercepted by the aryloxy to form acyl ammonium product cannot be ruled out. Such mechanistic alternatives could involve cyclisation through the sulfone oxygen,^[6] or *via* a cyclobutanone intermediate.^[30]

3.2 Kinetic Analysis

Having determined the temporal concentration of the reaction components, information concerning their reaction orders was sought. The inventive variable time normalization analysis (VTNA) reported by Burés was employed, which allows facile, rapid elucidation of reaction orders by using temporal concentration data.^[31] Kinetic analysis was carried out by performing seven different reactions, each with varying concentrations of ester **66** (120–180 mM), electrophile **31** (80–120 mM) and catalyst ^{19}F -**67** (16–24 mM). Visual analysis of the data was achieved by plotting the concentration of product **68** (sum of both diastereoisomers) against a time normalized axis of $\Sigma[\text{66}]^\alpha[\text{31}]^\beta[\text{67}]^\gamma\Delta t$. Subsequent variation of α , β and γ was

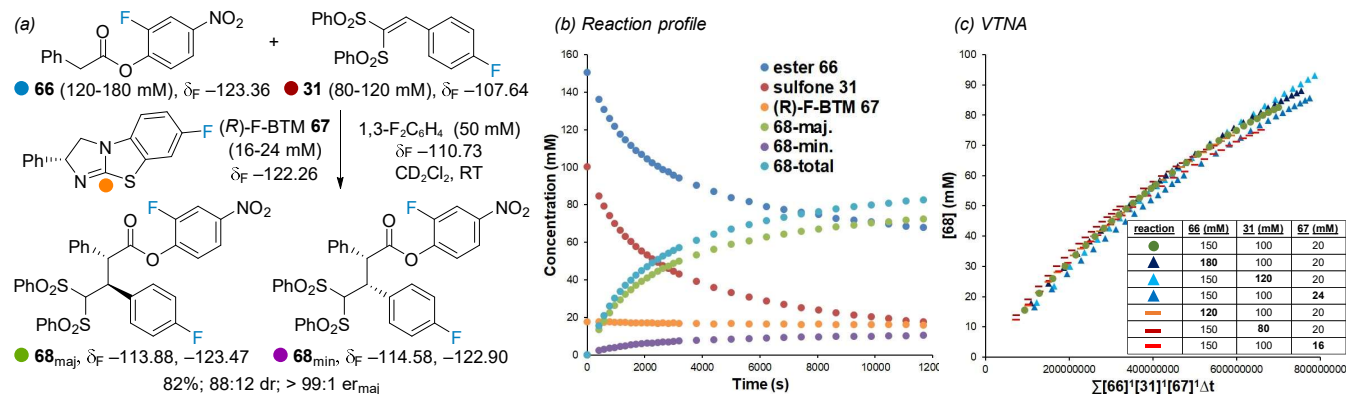


Figure 1. Mechanistic studies: (a) $^{19}\text{F}\{^1\text{H}\}$ NMR Spectroscopy for reaction mechanism analysis; (b) reaction profile using 150 mM **66**, 100 mM **31** and 20 mM **67**; (c) variable time normalization analysis, $\alpha = 1$, $\beta = 1$, and $\gamma = 1$.

carried out to achieve best overlay. Variation of α , β and γ at integer and half-integer values from 0 to 2 (see SI) showed best overlay when each component was set to 1. This is consistent with the reaction being first order in each of the three components, and indicates with the turnover-limiting step is likely to be either Michael addition or catalyst turnover (Figure 1c). Significantly, this mechanistic information contrasts our previous work regarding enantioselective Michael addition-lactonizations that utilized intramolecular catalyst turnover in ammonium enolate catalysis (Scheme 1).^[6] In this previous work, the process was found to be zero order in electrophile, with deprotonation of the acyl ammonium ion identified as the turnover-limiting step through a significant primary KIE. This is consistent with two mechanistically distinct scenarios being operative in these reactions.

3.3 Product Inhibition

Although reasonable overlay had been achieved, the observed curvature in Figure 1c indicates an additional variable, which has an effect of reducing the reaction rate over time, remained unaccounted for. As catalyst deactivation through protonation had already been included in the kinetic analysis, the potential for product inhibition was considered. Consistent with this hypothesis, incorporation of the product concentration into the time normalization approach $\Sigma[\mathbf{66}]^{\alpha}[\mathbf{31}]^{\beta}[\mathbf{67}]^{\gamma}[\mathbf{68}]^{\delta}\Delta t$, and arbitrarily setting $\delta = -0.2$ improved the linearity of the plot (see SI). A series of control reactions were therefore undertaken and compared to the standard reaction profile (Figure 2). Reactions with 20 mM product **68** added at the start of the reaction were carried out in triplicate, with the displayed profile an average of these three runs. It is clearly noticeable that the observed rate of vinyl bis-sulfone consumption is reduced in comparison to the standard reaction. Using the VTNA approach to estimate k_{obs} ,

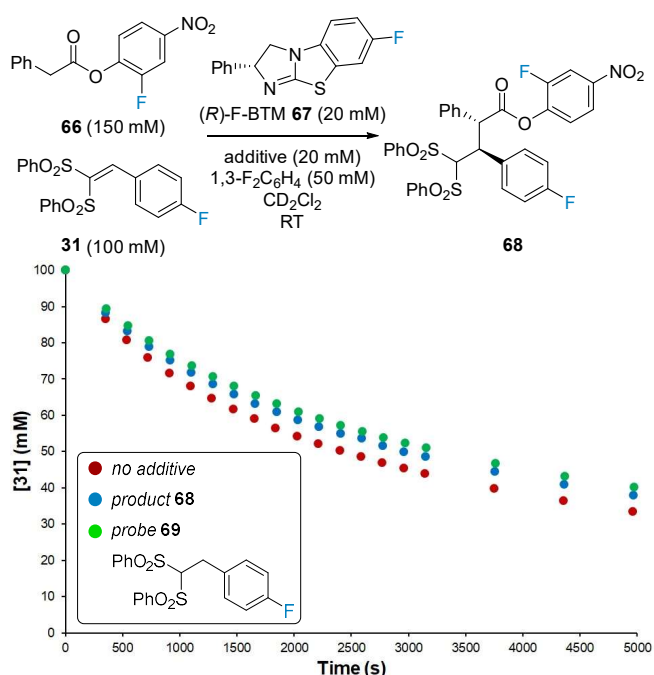
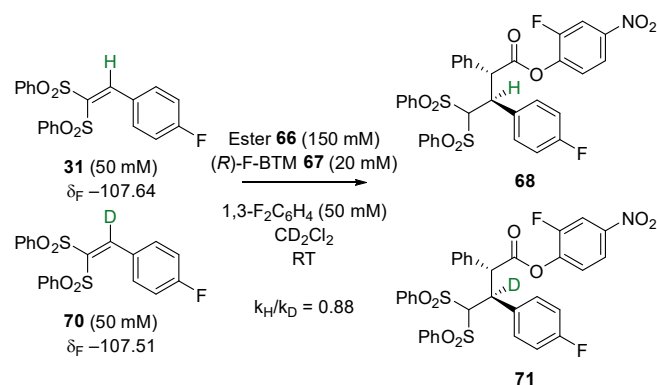


Figure 2. Product inhibition study.

the magnitude of k_{obs} was calculated to be 0.86 the magnitude of k_{obs} of the standard reaction (see SI). It was proposed the cause of the product inhibition could be the acidic proton adjacent to the bis-sulfone functionality. Consistent with this hypothesis, the addition of 20 mM of the saturated bis-sulfone **69** at the start of the reaction resulted in a similar retardation of the reaction rate. Using an identical protocol to that above, the magnitude of k_{obs} was calculated to be 0.80 the magnitude of k_{obs} of the standard reaction. Based on these results, it is postulated that the product may inhibit the reaction by protonating either the C(1)-ammonium enolate or aryloxide, thus retarding the rate of catalyst turnover.

3.4 Inverse Secondary Kinetic Isotope Effect

To further probe the reaction mechanism the leverage of a secondary kinetic isotope effect was investigated. The change in hybridization of an sp^2 -hybridized Michael acceptor to an sp^3 -hybridized product has previously been used to probe the turnover limiting step of Michael addition reactions through the observation of an inverse secondary kinetic isotope effect.^[32,33] We sought to generate this information through a direct competition experiment between enantioselective addition of ester **66** to a 50:50 ratio of isotopologues C(2)-H **31** ($\delta_{\text{F}} -107.64$) and C(2)-D **70** ($\delta_{\text{F}} -107.51$) in solution. Monitoring the relative rates of consumption of C(2)-H **31** and C(2)-D **70** in triplicate gave a kinetic isotope effect $k_{\text{H}}/k_{\text{D}} = 0.88$ (Scheme 5). For comparison, a similar effect ($k_{\text{H}}/k_{\text{D}} = 0.89$) was observed in separate independent parallel kinetic experiments using C(2)-H **31** and C(2)-D **70** (see SI). This information is consistent with the Michael addition being kinetically significant in this protocol and contrasts the intramolecular catalyst turnover approach in formal [4+2] cycloadditions, in which acyl ammonium deprotonation was observed to be turnover-limiting.^[6]

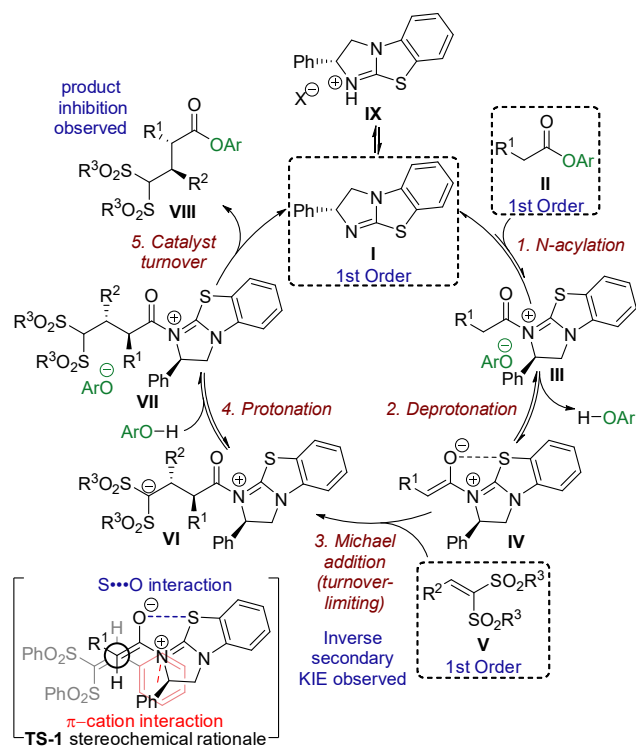


Scheme 5. Inverse secondary kinetic isotope effect.

3.5 Proposed Mechanism

Taking all the mechanistic information into account, the following mechanism is proposed (Scheme 6). The catalytic cycle starts by reversible *N*-acylation of free base BTM catalyst **I** with ester **II** to form acyl ammonium ion pair **III**. Reversible deprotonation of the acyl ammonium by the aryloxide counteranion affords the nucleophilic ammonium enolate **IV** and releases *para*-nitrophenol. It is proposed that a 1,5- $\text{O}\cdots\text{S}$ interaction (characterized as n_{O} to $\sigma^*_{\text{C-S}}$)^[34] lowers the rotational freedom of this intermediate, with the stereodirecting phenyl group forced to

adopt a pseudo-axial position to minimize 1,2-strain, and hence blocking the *Si* face of the enolate intermediate. Turnover rate-limiting Michael addition to the electrophile **V** on the *Re* face of the enolate leads to intermediate **VI**. Protonation by the *para*-nitrophenol released in step two gives acyl ammonium ion-pair **VII**. Addition of the aryloxide anion forms the product **VIII** and regenerates catalyst **I**, which is in equilibrium with the catalytically inactive protonated-BTM **IX**. Critical to the success of this protocol is the aryloxides ability to act as the leaving group, Brønsted base, Brønsted acid and nucleophile to turnover the catalyst, enabling the reaction to be carried out in the absence of auxiliary base. The observed diastereoselectivity can be rationalized tentatively by a favoured open pre-transition state assembly **TS-I** where gauche interactions are minimized about the forming C–C bond^[35] while allowing a potentially favourable π -cation interaction^[36] between the β -substituent of the bis-sulfone electrophile and the isothiuronium cation (Scheme 6). Interestingly, the relative configuration within the major diastereoisomer obtained using these bis-sulfone electrophiles is opposite to that observed in previous isothiurea catalysis employing intramolecular catalyst turnover processes (Scheme 1) and in the intermolecular addition to iminium ions (Scheme 2c). This difference can presumably be rationalized due to the two highly sterically demanding sulfone groups of this series of electrophile.



Scheme 6. Proposed Mechanism.

Conclusion

In conclusion, a base-free and proton neutral enantioselective Michael addition of ester pronucleophiles to vinyl bis-sulfones has been developed. This protocol, which can be carried out in

environmentally benign solvents, allows formation of α -alkylated products in excellent yield and with excellent diastereo- and enantioselectivity using low catalyst loadings (26 examples, up to 90:10 dr and $\geq 99:1$ er). Notably, no auxiliary base is required for this Michael addition process, with the key role of the aryloxide to act firstly as a leaving group, then a Brønsted base, a Brønsted acid and finally a Lewis base to promote catalyst turnover. The functional products can be deprotected upon treatment with Mg in MeOH to form α -alkylated amides without loss of stereointegrity. Mechanistic investigations using $^{19}\text{F}\{^1\text{H}\}$ NMR spectroscopy have enabled detailed investigation of the speciation within the reaction, with a variable time normalization analysis and an inverse secondary KIE indicative of Michael addition being the turnover-limiting step. Catalyst protonation, alongside product inhibition were also identified during this analysis. It is hoped that this mechanistic study will aid future reaction design in enantioselective ammonium enolate catalysis, and we are actively exploring these possibilities in our laboratory.^[37]

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Keywords: isothiurea catalysis • enantioselective Michael addition • base free / proton neutral • mechanistic analysis • VTNA • inverse secondary kinetic isotope effect

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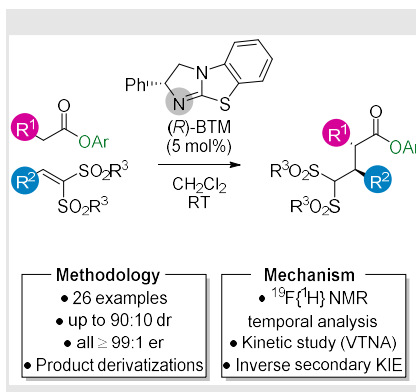
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Entry for the Table of Contents (Please choose one layout)

Layout 1:

RESEARCH ARTICLE

The base-free functionalization of aryl esters to form α -alkylated ester products in excellent enantioselectivity (>20 examples, all $\geq 99:1$ er) is developed using isothioureia catalysis. Key is the multifunctional role of the aryloxide, which operates as a leaving group, Brønsted base, Brønsted acid and Lewis base within the catalytic cycle. Mechanistic studies, including variable time normalization analysis and a kinetic isotope effect, were used to probe the reaction mechanism.



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